



October 18, 2017

U.S. Environmental Protection Agency  
Ariel Rios Building  
EPA Docket Center (ORD Docket)  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460

Submitted via the Federal eRulemaking Portal: <http://www.regulations.gov>

**Re: Availability of the Integrated Risk Information System (IRIS) Assessment Plans for Nitrate/Nitrite, Chloroform, and Ethylbenzene; Docket ID No.: EPAHQ-ORD-2017-0497 (82 Federal Register 43539, September 18, 2017)**

The American Chemistry Council<sup>1</sup> (ACC) Chlorine Chemistry Division<sup>2</sup> is pleased to submit these comments on EPA's National Center for Environmental Assessment (NCEA) draft IRIS Assessment Plan (IAP) for Chloroform.<sup>3,4</sup> ACC supports health assessments that reflect the best available science, utilize a weight of evidence process to evaluate the information, and apply transparent processes and approaches to support decision-making. ACC appreciates efforts by NCEA to be more transparent in the process utilized to develop the draft IAP for chloroform.

Following our review of the draft IAP for chloroform, we concur that focusing the IRIS reassessment on the health effects of chloroform via inhalation is appropriate, as is the development of a reference concentration (RfC). We offer the following recommendations as EPA moves forward:

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<sup>1</sup> ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a \$768 billion enterprise and a key element of the nation's economy. It is among the largest exports in the nation, accounting for 14 percent of all U.S. goods exports. Chemistry companies are among the largest investors in research and development, investing \$91 billion in 2016.

<sup>2</sup> The Chlorine Chemistry Division represents the major producers and users of chlorine in North America and works to promote and protect the sustainability of chlorine chemistry processes, products and applications.

<sup>3</sup> 82 Fed. Reg. 43539-43540 (September 18, 2017).

<sup>4</sup> [https://cfpub.epa.gov/ncea/iris\\_drafts/recorddisplay.cfm?deid=337469](https://cfpub.epa.gov/ncea/iris_drafts/recorddisplay.cfm?deid=337469).



1. The IRIS reassessment should use a weight-of-evidence approach to explicitly and transparently evaluate study quality, and use the study quality determination to integrate the data to draw conclusions regarding chloroform human health risk.
2. During the reassessment, it should be clearly noted that chloroform has a well-established mode of action (MOA) for carcinogenicity, which clearly demonstrates that chloroform exhibits a threshold. The MOA was established in 2001,<sup>5</sup> and as emphasized in the IAP, the MOA analysis concluded that:

chloroform is likely carcinogenic to humans by all routes of exposure **only** under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues. Based on this MOA analysis, the RfD [oral reference dose] was determined to be protective with respect to cancer because, at the RfD, cytotoxicity—a key event in the MOA for cancer—was not observed. The inhalation assessment posted in 1987 was never updated to address the route-to-route extrapolation approach or the more recent [2001] MOA analysis... **chloroform exhibits a “threshold” by all routes of exposure, and thus a chloroform dose that does not elicit cytotoxicity presents no cancer risk** [emphases added].<sup>6</sup>

3. When deriving an RfC, EPA should employ a physiologically based pharmacokinetic (PBPK) model and incorporate a non-linear dose response extrapolation, as supported by the data and the MOA.
4. EPA should also utilize the 2001 MOA analysis to determine whether a newly derived inhalation RfC is protective with respect to cancer, and if so, remove the current gavage- and linear extrapolation-based inhalation unit risk (IUR) value from the IRIS website. If not, data used in the reassessment should be evaluated to determine whether a revised IUR can be developed.
5. For the PECO (Populations, Exposures, Comparators, and Outcomes) element “populations,” cross-sectional and ecological epidemiology study designs should not be included with controlled exposure, cohort, and case-control designs as “most informative” for human exposures due to “ecological fallacy”<sup>7</sup> and other well-known limitations.

Lastly, for animal studies, ACC concurs with EPA’s decision to only include exposures to mixtures if they also include an “arm” with exposure to chloroform alone. EPA’s proposed

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<sup>5</sup> [https://cfpub.epa.gov/ncea/iris/iris\\_documents/documents/subst/0025\\_summary.pdf](https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0025_summary.pdf).

<sup>6</sup> Draft IAP for Chloroform, at 2.

<sup>7</sup> Dufault, B., and N. Klar. 2011. The quality of modern cross-sectional ecologic studies: a bibliometric review. *Am J Epidemiol.* 174(10): 1101–1107. Available: <https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kwr241>.



use of an iterative approach to identify and summarize non-mammalian and other mechanistic studies, “based on likelihood to impact evidence synthesis conclusions for human health” is warranted,<sup>8</sup> as is the conclusion “For chloroform, evaluating individual mechanistic studies for cancer-related outcomes is not anticipated to be critical because of the existing MOA analysis.”<sup>9</sup>

ACC appreciates consideration of these comments by EPA. If you have any questions, please feel free to contact me by phone at 202-249-6709 or via email at [judith\\_nordgren@americanchemistry.com](mailto:judith_nordgren@americanchemistry.com).

Sincerely,



Judith Nordgren  
Managing Director  
Chlorine Chemistry Division

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<sup>8</sup> Draft IAP for Chloroform, at 8.

<sup>9</sup> Id. at 6.

